REMARKS

Claims 1-8 stand rejected, and claims 9-29 stand withdrawn. Applicants respectfully request entry of the following amendments. Claim 2 is cancelled herein without prejudice. In addition, claims 1, 3-6, and 8 are amended herein to remove the references to rat. No new matter has been added.

In the event the Examiner refuses to enter the above amendment, Applicants requests entry of the above amendment upon filing of an appeal brief, in order to remove an issue for appeal.

In view of the amendments and remarks presented here, Applicants respectfully request reconsideration and allowance of claims 1 and 3-8.

Rejections under 35 U.S.C. § 112

The Examiner maintained in part the rejection of claims 1 and 3-8 under 35 U.S.C. § 112, first paragraph, alleging that the claims do not satisfy the enablement requirement. The Examiner asserted that Applicants' previous arguments and amendments were not persuasive to overcome the rejection concerning the alleged lack of enablement for making a transgenic rat as recited in the claims, at least in part because the prior art teaches that expression of the same gene in different animal species can result in different phenotypes.

Applicants disagree, for at least the reasons presented in the previous response. To further prosecution, however, Applicants have amended claims 1, 3-6, and 8 to remove the recitation of "rat." As acknowledged by the Examiner, the present claims are fully enabled.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1 and 3-8 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 1-7 under 35 U.S.C. § 103(a), alleging that they are unpatentable over the Grillot et al. reference (*J. Exp. Med.* (1996) 183:381-391), in view of the Adams et al. reference (*Nature* (1985) 318:533-538). The Examiner asserted that the motivation to combine the cited references is that the Ig heavy chain and kappa chain enhancers were demonstrated by Adams to be "capable of driving B cell specific heterologous transgene

expression in transgenic mice such that the substitution of one enhancer with the capacity to drive B cell specific heterologous transgene expression with another that shares the same property would have yielded the predictable result of transgenic [mice] with the claimed features." OA at page 5. The Examiner further asserted that the Adams et al. reference demonstrated that both the heavy chain and kappa chain enhancers effectively drive B cell specific heterologous transgene expression in transgenic mice, and that the rationale for combining the references is "simple substitution of one known element for another to obtain predictable results." *Ibid.* In addition, the Examiner asserted that the motivation to combine the teachings of cited references "need not be supported by a finding that the prior art suggested that the combination claimed by the applicant was the preferred, or most desirable combination over the other alternatives." OA at page 6.

The Examiner also maintained the rejection of claim 8 under 35 U.S.C. § 103(a), alleging that it is unpatentable over the Grillot et al. reference in view of the Adams et al. reference as applied to claims 1-7 above, and further in view of the Miller et al. reference (*Immunogenetics* (1992) 35:24-32).

Applicants respectfully traverse these rejections. First, as was known in the art at the time of Applicants' priority date, the Ig kappa and heavy chain enhancers are not simply interchangeable, as asserted by the Examiner. The inventors' own work has demonstrated that the two enhancers are active at different times during B cell development, with the kappa enhancer being activated later in B cell development than the heavy chain enhancer, which is active in early, pro, and pre B cells (Fulton and Van Ness (1994) *Nucl. Acids Res.* 22:4216-4223; Desig. ID AJJ on the PTO Form 1449 filed on October 6, 2006). The inventors' own work also has showed unique expression in late B cell and plasma cell stages when using the kappa enhancer (Fulton and Van Ness, *supra*; and Fulton and Van Ness (1993) *Nucl. Acids. Res.* 21:4941-4947; Desig. ID AKK on the PTO Form-1449 filed on October 6, 2006). Use of the heavy chain enhancer leads to earlier B cell malignancies that are not consistent with plasma cell malignancies. Thus, there was no *a priori* reason to assume both enhancers would activate transformation similarly. Accordingly, a unique discovery by the inventors was the malignant transformation of plasma cells by using the kappa enhancer.

The inventors also showed that combining the Ig promoter with the Ig 3' kappa enhancer provided specificity and higher expression. This had not been tested by others as of Applicants' priority date. Indeed, oncogene transformation of plasma cells did not occur unless the Ig promoter and the Ig 3' kappa enhancer were paired with the anti-apoptotic Bcl-xL construct developed by the inventors. As described in Applicants' specification, Bcl-xL expression significantly increased the number of plasma cells in the mice. See, for example, the specification at page 16, lines 5-29. Thus, the inventors' constructs combining the Ig promoter with the Ig 3' kappa enhancer have unique properties that allow for plasma cell expression not found in other pairings.

Second, Applicants again assert that the Adams et al. reference effectively teaches away from simply substituting the kappa enhancer for the heavy chain enhancer when the goal is promoting tumor growth. As noted in the response filed on January 23, 2009, the Adams et al. reference teaches that the heavy chain enhancer-myc construct resulted in higher tumor incidence than observed with the light chain enhancer-myc construct, suggesting that the heavy chain enhancer has greater activity than the light chain enhancer, at least with certain promoters, or has a larger pool of susceptible cells. Thus, a person of ordinary skill in the art reading the Adams et al. reference at the time of Applicants' priority date would not have been motivated to make the "simple substitution" alleged by the Examiner.

For at least these reasons, the presently recited mice are not obvious over the combination of cited references. In light of the above, Applicants respectfully request withdrawal of the rejections of claims 1 and 3-8 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that claims 1 and 3-8 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $245 for the Petition for Extension of Time fee, and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date: October 5, 2009

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